

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/SE05/000278

International filing date: 22 February 2005 (22.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: SE
Number: 0400523-7
Filing date: 01 March 2004 (01.03.2004)

Date of receipt at the International Bureau: 10 March 2005 (10.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

PCT / SE 2005 / 0 0 0 2 7 8

Intyg Certificate

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

(71) Sökande Gambro Lundia AB, Lund SE
Applicant (s)

(21) Patentansökningsnummer 0400523-7
Patent application number

(86) Ingivningsdatum 2004-03-01
Date of filing

Stockholm, 2005-03-01

För Patent- och registreringsverket
For the Patent- and Registration Office


Gunilla Larsson

Avgift
Fee

PATENT- OCH
REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

A MEDICAL SOLUTION, A METHOD FOR PRODUCING SAID MEDICAL
SOLUTION AND USE THEREOF

Technical field of the present invention

The present invention concerns a medical solution, a
method for producing said medical solution, a multi-
5 compartment bag containing the medical solution and the
use thereof.

Background of the invention

Medical solutions like dialysis solutions for
10 hemodialysis, hemofiltration, hemodiafiltration,
peritoneal dialysis, dialysis within renal intensive care
and liquids for substitution or infusion normally contain
a buffering substance. Often used buffers are acetate and
lactate buffers and these buffers are within the human
15 body metabolized into bicarbonate. Thus, the most
physiological buffer in medical solutions would be
bicarbonate.

However, the use of bicarbonate as a buffer is more
complicated than the use of acetate and lactate for two
20 reasons: First bicarbonate easily precipitates with one
of the essential elements in dialysis fluids, viz.
calcium, to form calcium carbonate, and second
bicarbonate solutions emit carbon dioxide and are thus
unstable.

25 One way to get around the precipitation problem is
to separate bicarbonate and calcium in two different
containers and then mix them just before use, but the
problem with the emitted carbon dioxide still remains.

If carbon dioxide leaves the bicarbonate solution
30 the result is an increase of pH up to 9-10,5 depending on
the original bicarbonate concentration. According to

2

Klasificering

prior art, this problem is solved either by use of a gas barrier for carbon dioxide or by allowing the bicarbonate to slowly equilibrate with the atmosphere.

5 If a gas barrier is used, a sensitive for leakage, complicated and expensive polymer is required as gas barrier otherwise it will result, after mixing with the rest of the content in the container, in a non-definable pH (depending of age of the solution).

10 The idea of letting the bicarbonate slowly equilibrate with the atmosphere is for example disclosed in US 6,309,673. However, this way of solving the problem creates an uncertainty concerning the pH value and the bicarbonate concentration in the final, ready-to-use solution.

15 In US 5,296,242 a solution is disclosed in which a premix of bicarbonate and carbonate is used in the buffer system. This document discloses a specific mix of bicarbonate and carbonate, which provides for a partial pressure of carbon dioxide that equals the physiological value of the partial pressure within the human body. The buffer solution is further combined with an acid solution, the acid being a metabolizable, organic acid. This reference stresses that an organic acid should be used, this for the therapy of acidosis.

25

Summary of the invention

An object of the invention is to provide a medical solution that, on one hand, ensures good stability, and on the other hand, ensures good biocompatibility.

30 The present invention provides a medical solution comprising at least two single solutions which, after terminal sterilization and up on use, can be mixed and used as a medical solution. The first single solution

comprises bicarbonate and carbonate in such proportions that the partial pressure of carbon dioxide, CO_2 , in the first single solution is in the same order of magnitude as the partial pressure of carbon dioxide, CO_2 , of the atmosphere. The second single solution comprises an acid and has a pH of 1,0-1,5. When said first and second single solutions, after terminal sterilization and up on use, are mixed a final solution, ready for use, is formed and it has a pH within the range of 7.0-7.6.

10 In a preferred embodiment of the present invention said first single solution has a pH of 10.1-10.5, preferably 10.3.

Said second single solution preferably has a pH of 1.3. Preferably, said second single solution is acidified by hydrochloric acid, HCl .

15 According to another preferred embodiment of the present invention the medical solution further comprises one or more osmotic agents. Preferred said one or more osmotic agents are chosen among glucose, glucose polymers, glycerol, xylitol, fructose, amino acids, peptides, proteins, amino sugars, N-acetyl glucose amine (NAG), or combinations thereof.

20 In one preferred embodiment of the present invention said one or more osmotic agents are, before being mixed into the final solution, arranged in said second single solution. In another preferred embodiment, said one or more osmotic agents are arranged in a third single solution before being mixed into the final solution. In even another preferred embodiment, said one or more osmotic agents are also arranged in a fourth single solution before being mixed into the final solution.

30 In a preferred embodiment, said one or more osmotic agents in said third and fourth single solutions is

glucose and/or glucose polymers; which could give rise to glucose degradation products (GDPs) during terminal sterilization and/or storage. If this is the case, said third and fourth single solutions comprise an acid and have a pH of at least 1.8, preferably at least 2.0, and a pH of at most 2.6, preferably at most 2.5, and most preferably at most 2.3.

According to another preferred embodiment of the present invention the final solution further comprises one or more electrolytes. The one or more electrolytes comprise according to one preferred embodiment of the invention one or more of the ions of sodium, calcium, potassium, magnesium and/or chloride. These one or more electrolytes could, according to different preferred embodiments of the present invention, before being mixed into the final solution, be included in said first single solution, in said second single solution, and/or in said optional third and/or fourth single solution.

In another preferred embodiment of the invention, the different single solutions are provided in different compartments in a multi-compartment bag before being mixed to the final solution.

The present invention further provides for a method for producing said medical solution. According to the invention the method comprises providing said single solutions in separate compartments, and thereafter terminally sterilizing said single solutions.

According to a preferred embodiment of the method according to the present invention said terminal sterilization is heat sterilization and/or radiation sterilization. In an even more preferred embodiment of the method according to the present invention, said

5

Patentavdelningen

terminal sterilization is heat sterilization at a temperature of at least 100°C, preferably at least 121 °C.

In a preferred embodiment of the invention said first and second single solutions, after sterilization and up on use, are mixed to form a final solution. In another preferred embodiment said first, second and third single solutions, after sterilization and up on use, are mixed to form a final solution. In another preferred embodiment of the invention, said first, second and fourth single solutions, after sterilization and up on use, are mixed to form a final solution, and in even another preferred embodiment of the invention, said first, second, third and fourth single solutions, after sterilization and up on use, are mixed to form a final solution.

The present invention further provides a multi-compartment bag comprising the medical solution according to above and the use of the medical solution according to above.

Additional objects, features, advantages and preferred embodiments of the present invention will become apparent from the following detailed description when taken in conjunction with the enclosed patent claims.

Definitions

The term "medical solution" is intended to mean dialysis solutions for hemodialysis, hemodiafiltration, hemofiltration, and peritoneal dialysis, solutions for dialysis within renal intensive care, solutions for substitution or infusion normally containing buffering substances, and solutions for nutrition purposes.

The term "single solution" is intended to mean one solution kept isolated from other solutions up until use.

The term "bicarbonate and carbonate" is intended to mean alkali bicarbonate and alkali carbonate, especially sodium bicarbonate and sodium carbonate.

The term "a final solution" is intended to mean the solution which includes the required different single solutions and which is ready for use.

The term "multi-compartment bag" is intended to mean bag divided into more than one compartment and that the content in the different compartments could be brought together and mixed before use.

The term "terminal sterilization" is intended to mean that the product is sterilized in its final package. The terminal sterilization may include heat sterilization and/or radiation sterilization, but is preferably heat sterilization effected in an autoclave at a temperature of at least 100°C, preferably at least 121°C.

The term "up on use" is intended to mean as close as possible before the medical solution is used for its specific purpose.

Detailed description of the invention

The medical solution according to the invention comprises a first single solution and a second single, wherein said first and second single solutions, after terminal sterilization and up on use, are to be mixed to form a final solution.

Said first single solution comprises bicarbonate and carbonate in such proportions that the partial pressure of carbon dioxide, CO₂, in the first single solution is of the same order of magnitude as the partial pressure of carbon dioxide, CO₂, of the atmosphere. Preferably,

bicarbonate and carbonate are mixed as sodium bicarbonate and sodium carbonate. Preferably, said first single solution has a pH within the range of 10.1-10.5, most preferably said first single solution has a pH of 10.3.

5 After having mixed at least said first and second single solutions into a final solution, said final solution has a pH within the range of 7.0-7.6. Further, said final solution preferably has a bicarbonate concentration of at least 25 mM, preferably at least
10 30 mM, and at most 45 mM, preferably at most 40 mM.

Said second single solution has preferably a pH within the range of 1.0-1.5, most preferably a pH of 1.3. In a preferred embodiment of the invention said second single solution comprises HCl.

15 The medical solution according to the invention preferably comprises one or more osmotic agents that are preferably chosen among glucose, glucose polymers, glycerol, xylitol, fructose, amino acids, peptides, proteins, amino sugars, N-acetyl glucose amine (NAG), or
20 combinations thereof. The one or more osmotic agents are in one preferred embodiment, before being mixed into the final solution, arranged in said second single solution. However, in another preferred embodiment the one or more osmotic agents are arranged in a third single solution.
25 In even another preferred embodiment of the invention, said one or more osmotic agents are, before being mixed into said final solution besides being arranged in a third single solution, also arranged in a fourth single solution.

30 In case of using one or more osmotic agents, which could give rise to glucose degradation products, said third and fourth single solutions further comprise an acid and preferably have a pH of at least 1.8, preferably

at least 2.0, and a pH of at most 2.6, preferably at most 2.5 and most preferably at most 2.3. Within these pH ranges the amount of the glucose degradation products (GDPs) being most toxic is as low as possible, and especially 3,4-dideoxyglucosone-3-ene (3,4-DGE), which is the most toxic one of all the GDPs. GDPs are known to give rise to several problems during for example peritoneal dialysis and of course it is always an aim to reduce the amount of toxic substances. However, besides optimizing the pH of said third single solution, it is also important to keep the concentration of one or more osmotic agents, which could give rise to GDPs, of at least 10 % by weight, preferably at least 20 % by weight and most preferably at least 40 % by weight, based on the total weight of said third or fourth single solution.

In a preferred embodiment of the invention said third and fourth single solutions could comprise different total amounts of one or more osmotic agents. The different total amounts could be achieved by providing the same concentrations within said third and fourth single solutions, but providing different volumes thereof. The different total amounts could also be achieved by providing the same volume of said third and fourth single solutions, but providing different concentrations in said third single solution in comparison with said fourth single solution. By having such a preferred medical solution comprising said first, second, third and fourth single solution, the user thereof could choose what concentration of osmotic agent the user would like to have for a specific treatment. By combining said first, second and third single solutions to a final solution, the user gets a first specific concentration of osmotic agent, by combining said first,

second and fourth single solution to a final solution, the user gets a second specific concentration of osmotic agent, and by combining said first, second, third and fourth single solutions to a final solution, the user
5 gets a third specific concentration of osmotic agent. Accordingly, said third and fourth single solutions could, up on use, be mixed individually, with said first and second solutions, i.e. either first, second and third, or first second and fourth, or jointly, i.e.
10 mixing first, second, third and fourth single solutions together. Note that said final solution always have a pH within the range of 7.0-7.6, no matter which of the above combinations of single solutions is used. The buffer solution in said first single solution have the
15 capability to buffer said third and/or fourth single solution(s) in combination with said first single solution to a final solution with a pH of 7.0-7.6.

In a preferred embodiment of the invention the medical solution further contains one or more
20 electrolytes. Preferably, the electrolytes is one or more of the ions of sodium, calcium, potassium, magnesium and chloride.

The arrangement of electrolytes in the different compartments is dependent on the different electrolytes
25 co-behavior with the other substances present in the single solutions, i.e. whether some sort of reaction could occur between one or more of the electrolyte(s) and the other substances present in a specific single solution. Usually, the electrolytes are contained in said
30 second single solution. For example, calcium ions are preferably provided in any of the other single solutions, but said first single solution. The reason for this is that calcium and bicarbonate together could cause

precipitation of calcium carbonate. However, calcium ions could be kept with bicarbonate under certain circumstances, such as specific pH ranges and so on, this is for example disclosed in EP 0 437 274, which hereby is
5 enclosed by reference.

In the method for producing a medical solution according to above, said single solutions are provided in separate compartments. Thereafter said single solutions are terminally sterilized. Preferably, the terminal sterilization is heat sterilization and/or radiation sterilization, (see also European Pharmacopoeia 1977 for a review of different sterilization techniques). In a preferred embodiment of the method according to the invention, the terminal sterilization is heat sterilization at a temperature of at least 100°C, preferably at least 121°C.

The sterilization time may vary depending on the sterilization temperature, the type of container and the contents therein to be sterilized.

20 The radiation sterilization may be either ionising or non-ionising sterilization. Examples of ionising sterilization are gamma and beta radiation. Examples of non-ionising radiation sterilization is UV radiation.

25 The medical solution according to the present invention has the advantage of ensuring good stability and good biocompatibility.

Said single solutions could be provided in different compartments in a multi-compartment bag, and the mixing could be provided by having the different compartments sealingly coupled by frangible pins, which different pins could be broken in order to mix the content in optional compartments within the multicompartment bag. The mixing could further be provided by having a peel seal in-

between the different compartments, which peal seals could be pealed in order to mix the content in the different compartments.

Below you will find different examples of solutions
5 according to the present invention.

Examples

By way of example, and not limitation, the following examples identify a variety of solutions made pursuant to an embodiment of the present invention.

Example 1 - 4

Two compartment bags

Compartment 1:

	Example 1	Example 2	Example 3	Example 4
NaHCO ₃	95,5 mM	95,5 mM	112 mM	112 mM
Na ₂ CO ₃	304,5 mM	304,5 mM	258 mM	258 mM
pH	10,3	10,3	10,3	10,3
Volume	0,5 l	0,5 l	0,5 l	0,5 l

Compartment 2:

	Example 1	Example 2	Example 3	Example 4
HCl	38 mM	38 mM	38 mM	38 mM
NaCl	77,3 mM	77,3 mM	77,3 mM	77,3 mM
CaCl ₂ *2H ₂ O	1,95 mM	1,95 mM	1,95 mM	1,95 mM
MgCl ₂ *6 H ₂ O	0,56 mM	0,56 mM	0,56 mM	0,56 mM
Glucose	-	1,22 g/l	-	1,22 g/l
Lactate	-	-	3,30 mM	3,30 mM
pH	1,3	1,3	1,3	1,3
Volume	4,5 l	4,5 l	4,5 l	4,5 l

Solution, mixed and ready for use:

	Example 1	Example 2	Example 3	Example 4
Volume	5 l	5 l	5 l	5 l
pH	7,25	7,25	7,25	7,25
Cl ⁻	108,3 mM	108,3 mM	108,3 mM	108,3 mM
Na ⁺	140,02 mM	140,02 mM	135,37 mM	135,37 mM
Ca ⁺	1,76 mM	1,76 mM	1,76 mM	1,76 mM
Mg ⁺	0,5 mM	0,5 mM	0,5 mM	0,5 mM
HCO ₃ ⁻	40 mM	40 mM	37 mM	37 mM
Glucose	-	1,1 g/l	-	1,1 g/l
Lactate	-	-	3 mM	3 mM

Example 5-8

Two compartment bags

5

Compartment 1:

	Example 5	Example 6	Example 7	Example 8
NaHCO ₃	139 mM	139 mM	133 mM	133 mM
Na ₂ CO ₃	661 mM	661 mM	607 mM	607 mM
pH	10,3	10,3	10,3	10,3
Volume	0,25 l	0,25 l	0,25 l	0,25 l

Compartment 2:

	Example 5	Example 6	Example 7	Example 8
HCl	38,4 mM	38,4 mM	38,4 mM	38,4 mM
NaCl	70,5 mM	70,5 mM	70,5 mM	70,5 mM
CaCl ₂ *2H ₂ O	1,84 mM	1,84 mM	1,84 mM	1,84 mM
MgCl ₂ *6 H ₂ O	0,53 mM	0,53 mM	0,53 mM	0,53 mM
Glucose	-	1,16 g/l	-	1,16 g/l
Lactate	-	-	3,16 mM	3,16 mM
pH	1,3	1,3	1,3	1,3
Volume	4,75 l	4,75 l	4,75 l	4,75 l

13

Solution, mixed and ready for use:

	Example 5	Example 6	Example 7	Example 8
Volume	5 l	5 l	5 l	5 l
pH	7,25	7,25	7,25	7,25
Cl ⁻	107,6 mM	107,6 mM	107,6 mM	107,6 mM
Na ⁺	140,03 mM	140,03 mM	137,18 mM	137,18 mM
Ca ⁺	1,75 mM	1,75 mM	1,75 mM	1,75 mM
Mg ⁺	0,5 mM	0,5 mM	0,5 mM	0,5 mM
HCO ₃ ⁻	40 mM	40 mM	37 mM	37 mM
Glucose	-	1,1 g/l	-	1,1 g/l
Lactate	-	-	3 mM	3 mM

Examples 9-12

Three compartment bags:

5

Compartment 1:

	Example 9	Example 10	Example 11	Example 12
NaHCO ₃	95,5 mM	112 mM	139 mM	133 mM
Na ₂ CO ₃	304,5 mM	258 mM	661 mM	607 mM
pH	10,3	10,3	10,3	10,3
Volume	0,2 l	0,2 l	0,1 l	0,1 l

Compartment 2:

	Example 9	Example 10	Example 11	Example 12
HCl	41,02 mM	41,02 mM	39,23 mM	39,23mM
NaCl	83,45 mM	83,45 mM	72,02 mM	72,02 mM
CaCl ₂ *2H ₂ O	2,11 mM	2,11 mM	1,88 mM	1,88 mM
MgCl ₂ *6 H ₂ O	0,60 mM	0,60 mM	0,54 mM	0,54 mM
Glucose	17,05	17,05 g/l	16,13 g/l	16,13 g/l
Lactate	-	3,41 mM	-	3,23 mM
pH	1,3	1,3	1,3	1,3
Volume	1,76 l	1,76 l	1,86 l	1,86 l

Third compartment:

	Example 9	Example 10	Example 11	Example 12
Glucose	500 g/l	500 g/l mM	500 g/lmM	500 g/l
pH	2-2,5	2-2,5	2-2,5	2-2,5
Volume	0,04 l	0,04 l	0,04 l	0,04 l

Solution, mixed and ready for use:

	Example 9	Example 10	Example 11	Example 12
Volume	2 l	2 l	2 l	2 l
pH	7,25	7,25	7,25	7,25
Cl ⁻	108,3 mM	108,3 mM	107,96 mM	107,96 mM
Na ⁺	140,02 mM	135,37 mM	140,03 mM	140,03 mM
Ca ⁺	1,76 mM	1,76 mM	1,75 mM	1,75 mM
Mg ⁺	0,5 mM	0,5 mM	0,5 mM	0,5 mM
HCO ₃ ⁻	40 mM	37 mM	40 mM	40 mM
Glucose	15/25 g/l*	15/25 g/l*	15/25 g/l*	15/25 g/l*
Lactate	-	3 mM	-	3 mM

5

* 15 g/l is compartment 1 and 2 are mixed and 25 g/l if all three compartments are mixed.

Examples 13-16

10

Four-compartment bags:

Compartment 1:

	Example 13	Example 14	Example 15	Example 16
NaHCO ₃	95,5 mM	112 mM	139 mM	133 mM
Na ₂ CO ₃	304,5 mM	258 mM	661 mM	607 mM
pH	10,3	10,3	10,3	10,3
Volume	0,196 l	0,196 l	0,098 l	0,098 l

15

Compartment 2:

	Example 13	Example 14	Example 15	Example 16
HCl	38,78 mM	38,78 mM	39,18 mM	39,18 mM
NaCl	78,88 mM	78,88 mM	71,94 mM	71,94 mM
CaCl ₂ *2H ₂ O	1,99 mM	1,99 mM	1,88 mM	1,88 mM
MgCl ₂ *6 H ₂ O	0,57 mM	0,57 mM	0,54 mM	0,54 mM
Lactate	-	3,41 mM	-	3,22 mM
pH	1,3	1,3	1,3	1,3
Volume	1,764 l	1,764 l	1,862 l	1,862 l

Third compartment:

	Example 13	Example 14	Example 15	Example 16
Glucose	500 g/l	500 g/l	500 g/l	500 g/l
pH	2-2,5	2-2,5	2-2,5	2-2,5
Volume	0,062 l	0,062 l	0,062 l	0,062 l

5 Fourth compartment:

	Example 13	Example 14	Example 15	Example 16
Glucose	500 g/l	500 g/l	500 g/l	500 g/l
pH	2-2,5	2-2,5	2-2,5	2-2,5
Volume	0,103 l	0,103 l	0,103 l	0,103 l

16

Solution, mixed and ready for use:

Example 13	Compartment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,25	7,25	7,25
Cl ⁻	107,1 mM	105,0 mM	101,9 mM
Na ⁺	137,1 mM	134,4 mM	130,5 mM
Ca ⁺	1,74 mM	1,70 mM	1,65 mM
Mg ⁺	0,50 mM	0,49 mM	0,47 mM
HCO ₃ ⁻	38,8 mM	38,0 mM	36,9 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l

Example 14	Compartment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,25	7,25	7,25
Cl ⁻	107,1 mM	105,0 mM	101,9 mM
Na ⁺	135,6 mM	132,9 mM	129,1 mM
Ca ⁺	1,74 mM	1,70 mM	1,65 mM
Mg ⁺	0,50 mM	0,49 mM	0,47 mM
HCO ₃ ⁻	35,9 mM	35,2 mM	34,1 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l
Lactate	2,98 mM	2,92 mM	2,83 mM

17

Example 15	Compartment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,25	7,25	7,25
Cl ⁻	106,8 mM	104,7mM	101,6 mM
Na ⁺	137,1 mM	134,3 mM	130,5 mM
Ca ⁺	1,73 mM	1,70 mM	1,65 mM
Mg ⁺	0,50 mM	0,49 mM	0,47 mM
HCO ₃ ⁻	38,8 mM	38,0 mM	36,9 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l

Example 16	Compartment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,25	7,25	7,25
Cl ⁻	106,8 mM	104,7 mM	101,6 mM
Na ⁺	137,5 mM	134,7 mM	130,8 mM
Ca ⁺	1,73 mM	1,70 mM	1,65 mM
Mg ⁺	0,5 mM	0,49 mM	0,47 mM
HCO ₃ ⁻	38,8 mM	38,0 mM	36,9 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l
Lactate	2,97 mM	2,91 mM	2,82 mM

Example 17-20

5 Two compartment bags

Compartment 1:

	Example 17	Example 18	Example 19	Example 20
NaHCO ₃	95,5 mM	95,5 mM	112 mM	112 mM
Na ₂ CO ₃	304,5 mM	304,5 mM	258 mM	258 mM
pH	10,3	10,3	10,3	10,3
Volume	0,5 l	0,5 l	0,5 l	0,5 l

18

Compartment 2:

	Example 17	Example 18	Example 19	Example 20
HCl	35,5 mM	35,5 mM	35,5 mM	35,5 mM
NaCl	77,3 mM	77,3 mM	77,3 mM	77,3 mM
CaCl ₂ *2H ₂ O	1,95 mM	1,95 mM	1,95 mM	1,95 mM
MgCl ₂ *6 H ₂ O	0,56 mM	0,56 mM	0,56 mM	0,56 mM
Glucose	-	1,22 g/l	-	1,22 g/l
Lactate	-	-	3,30 mM	3,30 mM
pH	1,3	1,3	1,3	1,3
Volume	4,5 l	4,5 l	4,5 l	4,5 l

Solution, mixed and ready for use:

	Example 17	Example 18	Example 19	Example 20
Volume	5 l	5 l	5 l	5 l
pH	7,5	7,5	7,5	7,5
Cl ⁻	106,03 mM	106,03 mM	106,03 mM	106,03 mM
Na ⁺	140,02 mM	140,02 mM	135,37 mM	135,37 mM
Ca ⁺	1,76 mM	1,76 mM	1,76 mM	1,76 mM
Mg ⁺	0,5 mM	0,5 mM	0,5 mM	0,5 mM
HCO ₃ ⁻	40 mM	40 mM	37 mM	37 mM
Glucose	-	1,1 g/l	-	1,1 g/l
Lactate	-	-	3 mM	3 mM

5 Example 21-24

Two compartment bags

Compartment 1:

	Example 21	Example 22	Example 23	Example 24
NaHCO ₃	139 mM	139 mM	133 mM	133 mM
Na ₂ CO ₃	661 mM	661 mM	607 mM	607 mM
pH	10,3	10,3	10,3	10,3
Volume	0,25 l	0,25 l	0,25 l	0,25 l

19

Compartment 2:

	Example 21	Example 22	Example 23	Example 24
HCl	36,11 mM	36,11 mM	36,11 mM	36,11 mM
NaCl	70,5 mM	70,5 mM	70,5 mM	70,5 mM
CaCl ₂ *2H ₂ O	1,84 mM	1,84 mM	1,84 mM	1,84 mM
MgCl ₂ *6 H ₂ O	0,53 mM	0,53 mM	0,53 mM	0,53 mM
Glucose	-	1,16 g/l	-	1,16 g/l
Lactate	-	-	3,16 mM	3,16 mM
pH	1,3	1,3	1,3	1,3
Volume	4,75 l	4,75 l	4,75 l	4,75 l

Solution, mixed and ready for use:

	Example 21	Example 22	Example 23	Example 24
Volume	5 l	5 l	5 l	5 l
pH	7,5	7,5	7,5	7,5
Cl ⁻	105,78 mM	105,78 mM	105,78 mM	105,78 mM
Na ⁺	140,03 mM	140,03 mM	137,18 mM	137,18 mM
Ca ⁺	1,75 mM	1,75 mM	1,75 mM	1,75 mM
Mg ⁺	0,5 mM	0,5 mM	0,5 mM	0,5 mM
HCO ₃ ⁻	40 mM	40 mM	37 mM	37 mM
Glucose	-	1,1 g/l	-	1,1 g/l
Lactate	-	-	3 mM	3 mM

5

Example 25-28

Two compartment bags

Compartment 1:

	Example 25	Example 26	Example 27	Example 28
NaHCO ₃	95,5 mM	95,5 mM	112 mM	112 mM
Na ₂ CO ₃	304,5 mM	304,5 mM	258 mM	258 mM
pH	10,3	10,3	10,3	10,3
Volume	0,5 l	0,5 l	0,5 l	0,5 l

5

Compartment 2:

	Example 25	Example 26	Example 27	Example 28
HCl	38,74 mM	38,74 mM	38,74 mM	38,74 mM
NaCl	77,3 mM	77,3 mM	77,3 mM	77,3 mM
CaCl ₂ *2H ₂ O	1,95 mM	1,95 mM	1,95 mM	1,95 mM
MgCl ₂ *6 H ₂ O	0,56 mM	0,56 mM	0,56 mM	0,56 mM
Glucose	-	1,22 g/l	-	1,22 g/l
Lactate	-	-	3,30 mM	3,30 mM
pH	1,3	1,3	1,3	1,3
Volume	4,5 l	4,5 l	4,5 l	4,5 l

Solution, mixed and ready for use:

	Example 25	Example 26	Example 27	Example 28
Volume	5 l	5 l	5 l	5 l
pH	7,0	7,0	7,0	7,0
Cl ⁻	108,95 mM	108,95 mM	108,95 mM	108,95 mM
Na ⁺	140,02 mM	140,02 mM	135,37 mM	135,37 mM
Ca ⁺	1,76 mM	1,76 mM	1,76 mM	1,76 mM
Mg ⁺	0,5 mM	0,5 mM	0,5 mM	0,5 mM
HCO ₃ ⁻	40 mM	40 mM	37 mM	37 mM
Glucose	-	1,1 g/l	-	1,1 g/l
Lactate	-	-	3 mM	3 mM

Example 29-32

Two compartment bags

5 Compartment 1:

	Example 29	Example 30	Example 31	Example 32
NaHCO ₃	139 mM	139 mM	133 mM	133 mM
Na ₂ CO ₃	661 mM	661 mM	607 mM	607 mM
pH	10,3	10,3	10,3	10,3
Volume	0,25 l	0,25 l	0,25 l	0,25 l

Compartment 2:

	Example 29	Example 30	Example 31	Example 32
HCl	39,19 mM	39,19 mM	39,19 mM	39,19 mM
NaCl	70,5 mM	70,5 mM	70,5 mM	70,5 mM
CaCl ₂ *2H ₂ O	1,84 mM	1,84 mM	1,84 mM	1,84 mM
MgCl ₂ *6 H ₂ O	0,53 mM	0,53 mM	0,53 mM	0,53 mM
Glucose	-	1,16 g/l	-	1,16 g/l
Lactate	-	-	3,16 mM	3,16 mM
pH	1,3	1,3	1,3	1,3
Volume	4,75 l	4,75 l	4,75 l	4,75 l

22

Solution, mixed and ready for use:

	Example 29	Example 30	Example 31	Example 32
Volume	5 l	5 l	5 l	5 l
pH	7,0	7,0	7,0	7,0
Cl ⁻	108,71 mM	108,71 mM	108,71 mM	108,71 mM
Na ⁺	140,03 mM	140,03 mM	137,18 mM	137,18 mM
Ca ⁺	1,75 mM	1,75 mM	1,75 mM	1,75 mM
Mg ⁺	0,5 mM	0,5 mM	0,5 mM	0,5 mM
HCO ₃ ⁻	40 mM	40 mM	37 mM	37 mM
Glucose	-	1,1 g/l	-	1,1 g/l
Lactate	-	-	3 mM	3 mM

Examples 33-36

5 Four-compartment bags:

Compartment 1:

	Example 33	Example 34	Example 35	Example 36
NaHCO ₃	95,5 mM	112 mM	139 mM	133 mM
Na ₂ CO ₃	304,5 mM	258 mM	661 mM	607 mM
pH	10,3	10,3	10,3	10,3
Volume	0,196 l	0,196 l	0,098 l	0,098 l

Compartment 2:

	Example 33	Example 34	Example 35	Example 36
HCl	38,74 mM	38,74 mM	39,19 mM	39,19 mM
NaCl	78,88 mM	78,88 mM	71,94 mM	71,94 mM
CaCl ₂ *2H ₂ O	1,99 mM	1,99 mM	1,88 mM	1,88 mM
MgCl ₂ *6 H ₂ O	0,57 mM	0,57 mM	0,54 mM	0,54 mM
Lactate	-	3,41 mM	-	3,22 mM
pH	1,3	1,3	1,3	1,3
Volume	1,764 l	1,764 l	1,862 l	1,862 l

23

Third compartment:

	Example 33	Example 34	Example 35	Example 36
Glucose	500 g/l	500 g/l	500 g/l	500 g/l
pH	2-2,5	2-2,5	2-2,5	2-2,5
Volume	0,062 l	0,062 l	0,062 l	0,062 l

Fourth compartment:

	Example 33	Example 34	Example 35	Example 36
Glucose	500 g/l	500 g/l	500 g/l	500 g/l
pH	2-2,5	2-2,5	2-2,5	2-2,5
Volume	0,103 l	0,103 l	0,103 l	0,103 l

5 Solution, mixed and ready for use:

Example 33	Compartment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,0	7,0	7,0
Cl ⁻	107,8 mM	105,6 mM	102,5 mM
Na ⁺	137,1 mM	134,4 mM	130,5 mM
Ca ⁺	1,74 mM	1,70 mM	1,65 mM
Mg ⁺	0,50 mM	0,49 mM	0,47 mM
HCO ₃ ⁻	38,8 mM	38,0 mM	36,9 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l

24

Example 34	Compartment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,0	7,0	7,0
Cl ⁻	107,8 mM	105,6 mM	102,5 mM
Na ⁺	135,6 mM	132,9 mM	129,1 mM
Ca ⁺	1,74 mM	1,70 mM	1,65 mM
Mg ⁺	0,50 mM	0,49 mM	0,47 mM
HCO ₃ ⁻	35,9 mM	35,2 mM	34,1 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l
Lactate	2,98 mM	2,92 mM	2,83 mM

Example 35	Compartment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,0	7,0	7,0
Cl ⁻	113,2 mM	110,9mM	107,7 mM
Na ⁺	137,1 mM	134,3 mM	130,5 mM
Ca ⁺	1,73 mM	1,70 mM	1,65 mM
Mg ⁺	0,50 mM	0,49 mM	0,47 mM
HCO ₃ ⁻	38,8 mM	38,0 mM	36,9 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l

25

Example 36	Compartment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,0	7,0	7,0
Cl ⁻	113,2 mM	110,9 mM	107,7 mM
Na ⁺	137,5 mM	134,7 mM	130,8 mM
Ca ⁺	1,73 mM	1,70 mM	1,65 mM
Mg ⁺	0,5 mM	0,49 mM	0,47 mM
HCO ₃ ⁻	38,8 mM	38,0 mM	36,9 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l
Lactate	2,97 mM	2,91 mM	2,82 mM

Examples 37-40

Four-compartment bags:

5

Compartment 1:

	Example 37	Example 38	Example 39	Example 40
NaHCO ₃	95,5 mM	112 mM	139 mM	133 mM
Na ₂ CO ₃	304,5 mM	258 mM	661 mM	607 mM
pH	10,3	10,3	10,3	10,3
Volume	0,196 l	0,196 l	0,098 l	0,098 l

Compartment 2:

	Example 37	Example 38	Example 39	Example 40
HCl	35,49 mM	35,49 mM	36,11 mM	36,11 mM
NaCl	78,88 mM	78,88 mM	71,94 mM	71,94 mM
CaCl ₂ *2H ₂ O	1,99 mM	1,99 mM	1,88 mM	1,88 mM
MgCl ₂ *6 H ₂ O	0,57 mM	0,57 mM	0,54 mM	0,54 mM
Lactate	-	3,41 mM	-	3,22 mM
pH	1,3	1,3	1,3	1,3
Volume	1,764 l	1,764 l	1,862 l	1,862 l

26

Third compartment:

	Example 37	Example 38	Example 39	Example 40
Glucose	500 g/l	500 g/l	500 g/l	500 g/l
pH	2-2,5	2-2,5	2-2,5	2-2,5
Volume	0,062 l	0,062 l	0,062 l	0,062 l

Fourth compartment:

	Example 37	Example 38	Example 39	Example 40
Glucose	500 g/l	500 g/l	500 g/l	500 g/l
pH	2-2,5	2-2,5	2-2,5	2-2,5
Volume	0,103 l	0,103 l	0,103 l	0,103 l

5 Solution, mixed and ready for use:

Example 37	Compartment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,5	7,5	7,5
Cl ⁻	104,9 mM	102,8 mM	99,8 mM
Na ⁺	137,1 mM	134,4 mM	130,5 mM
Ca ⁺	1,74 mM	1,70 mM	1,65 mM
Mg ⁺	0,50 mM	0,49 mM	0,47 mM
HCO ₃ ⁻	38,8 mM	38,0 mM	36,9 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l

27

Example 38	Compartment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,5	7,5	7,5
Cl ⁻	104,9 mM	102,8 mM	99,8 mM
Na ⁺	135,6 mM	132,9 mM	129,1 mM
Ca ⁺	1,74 mM	1,70 mM	1,65 mM
Mg ⁺	0,50 mM	0,49 mM	0,47 mM
HCO ₃ ⁻	35,9 mM	35,2 mM	34,1 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l
Lactate	2,98 mM	2,92 mM	2,83 mM

Example 39	Compartment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,5	7,5	7,5
Cl ⁻	110,1 mM	107,9 mM	104,8 mM
Na ⁺	137,1 mM	134,3 mM	130,5 mM
Ca ⁺	1,73 mM	1,70 mM	1,65 mM
Mg ⁺	0,50 mM	0,49 mM	0,47 mM
HCO ₃ ⁻	38,8 mM	38,0 mM	36,9 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l

28

Example 40	Compartment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,5	7,5	7,5
Cl ⁻	110,1 mM	107,9 mM	104,8 mM
Na ⁺	137,5 mM	134,7 mM	130,8 mM
Ca ⁺	1,73 mM	1,70 mM	1,65 mM
Mg ⁺	0,5 mM	0,49 mM	0,47 mM
HCO ₃ ⁻	38,8 mM	38,0 mM	36,9 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l
Lactate	2,97 mM	2,91 mM	2,82 mM

In summary, based on the above results, the inventors concluded that a stable and biocompatible bicarbonate-based solution can be prepared, provided that it comprises bicarbonate and carbonate in such proportions that the partial pressure of carbon dioxide, CO₂, is in the same order of magnitude as the partial pressure of CO₂ of the atmosphere.

It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

CLAIMS

1. A medical solution comprising
 - 5 a first single solution comprising bicarbonate and carbonate in such proportions that the partial pressure of carbon dioxide, CO₂, in the first single solution is of the same order of magnitude as the partial pressure of carbon dioxide, CO₂, of the atmosphere, and
 - 10 a second single solution comprising an acid, wherein said first and second single solutions, after terminal sterilization and up on use, are to be mixed to form a final solution; wherein said second single solution has a pH of 1.0-1.5, and wherein the said
 - 15 final solution has a pH of 7.0-7.6.
2. A medical solution according to claim 1, wherein said first single solution has a pH of 10.1-10.5, preferably 10.3.
3. A medical solution according to any of claim 1 or
- 20 2, wherein said second single solution has a pH of 1.3.
4. A medical solution according to anyone of the previous claims, wherein the second single solution comprises HCl.
5. A medical solution according to any one of the
- 25 previous claims, wherein the medical solution further comprises one or more osmotic agents.
6. A medical solution according to claim 5, wherein said one or more osmotic agents are chosen among glucose, glucose polymers, glycerol, xylitol, fructose, amino
- 30 acids, peptides, proteins, amino sugars, N-acetyl glucose amine (NAG), or combinations thereof.
7. A medical solution according to claim 5, wherein the one or more osmotic agents, before being mixed into

30

the final solution, are arranged in said second single solution.

8. A medical solution according to claim 5, wherein said one or more osmotic agent, before being mixed into said final solution, are arranged in a third single solution.

9. A medical solution according to claim 8, wherein said one or more osmotic agent also are arranged in a fourth single solution.

10. 10. A medical solution according to claim 8 or 9, wherein said one or more osmotic agents in said third and/or fourth single solution is glucose and/or glucose polymers giving rise to glucose degradation products (GDPs) during terminal sterilization and/or storage, and wherein said third and/or fourth single solutions comprise an acid and has a pH of at least 1.8, preferably at least 2.0, and a pH of at most 2.6, preferably at most 2.5, and most preferably at most 2.3.

11. A medical solution according to anyone of the previous claims, wherein the medical solution further comprises one or more electrolytes.

12. A medical solution according to claim 11, wherein said one ore more electrolytes comprise one or more of the ions of sodium, calcium, potassium, magnesium and/or chloride.

13. A medical solution according to claim 11 or 12, wherein one or more electrolytes, before being mixed into the final solution, is/are arranged in said first single solution.

14. A medical solution according to any of claims 11-13, wherein one or more electrolytes, before being mixed into the final solution, is/are arranged in said second single solution.

32

23. A method according to any of claims 17-19, wherein said first, second, third and fourth single solutions, after terminal sterilization and up on use, are mixed to form a final solution.

5 24. A method according to any of claims 17-23, wherein the different single solutions are provided in different compartments in a multi-compartment bag before being mixed to the final solution.

10 25. A multi-compartment bag comprising the medical solution according to any one of claims 1-16.

26. A use of a medical solution according to any one of claims 1-16.

ABSTRACT

The present invention relates to a medical solution, a method for producing said medical solution, a multi-compartment bag containing the medical solution as well as use of said medical solution. According to the invention the medical solution comprises a first single solution comprising bicarbonate and carbonate in such proportions that the partial pressure of carbon dioxide, CO₂, in the first single solution is of the same order of magnitude as the partial pressure of carbon dioxide, CO₂, of the atmosphere. The medical solution further comprises a second single solution comprising an acid. Said first and second single solutions are, after terminal sterilization and up on use, to be mixed to form a final solution. Said second single solution has a pH of 1.0-1.5, and said final solution has a pH of 7.0-7.6.